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ORIGINAL ARTICLE

The pre- and post-authorisation data published by the European medicines agency on the use of biologics during pregnancy and lactation

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Aims: The effects of biologics on reproduction/lactation are mostly unknown although many patients that receive biologics are women of reproductive age. The first objective of this study was to investigate the publicly available data on pregnancy/lactation before and after marketing authorization in Europe of biologics for the indications of rheumatologic inflammatory autoimmune diseases and inflammatory bowel disease. Secondary objectives included the assessment of the clinical relevance of the provided data and comparison of initial and post-authorization data.

Methods: Initial and post-authorization data were extracted from the European Public Assessment Reports and the latest versions of Summary of Product Characteristics using publicly available documents on the European Medicines Agency's website. Four sections were categorized regarding pregnancy outcomes: pre-clinical/animal studies, human female fertility, pregnancy-related outcomes and congenital malformations in the human fetus. Three sections were categorized regarding lactation outcomes: pre-clinical/animal studies, excretion in human breast milk and absorption in children through breastfeeding. The clinical applicability of each category was scored by specified criteria, based on scientific literature, and further as defined by the authors.

Results: For the 16 included biologics, post-authorization data were delivered only for adalimumab, certolizumab pegol, etanercept and infliximab. For the 12 remaining biologics limited data on pregnancy and lactation during the post-marketing period of 2–21 years were available.

Conclusions: In this article several suggestions are provided for improving a multi-disciplinary approach to these issues. The initiation of suitable registries by marketing authorization holders and data transparency for clinicians and academics are highly endorsed.

The authors confirm that no Principal Investigator for this paper was involved, as no patients have participated in the study.

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KEYWORDS

biologics, gastroenterology, lactation, pregnancy, rheumatology

1 | INTRODUCTION

Biologics are widely used in rheumatologic and gastroenterological inflammatory autoimmune diseases. Their use in women of childbearing potential is expected and subsequently detailed information on the impact of these drugs on reproduction is therefore of utmost importance.¹

In Europe, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the European Medicines Agency (EMA) established rules to report on the reproductive safety of (approved) drugs. These rules include the ICH-S5 guideline (1993, discusses detection of toxicity to reproduction mostly in preclinical/animal studies), the ICH-S6 guideline (2011, recommends a basic framework for the preclinical safety evaluation of biotechnology-derived pharmaceuticals), the EMA "Guideline on the exposure to medicinal products during pregnancy: Need for post-authorisation data" (2006) and the "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling" (2009).²⁻¹⁰

All these guidelines provide a minimum framework for the pharmaceutical industry to perform pregnancy- and fertility-related studies before and after registration.

Our first objective was to investigate the data on pregnancy and lactation made publicly available by pharmaceutical companies at the time and after marketing authorization in Europe of biologics for the indications of rheumatologic and inflammatory bowel diseases. Secondary objectives included the assessment of the clinical relevance of the provided data and comparison of the initial provided data to post-authorization data. It should be noted that this study is not a review of the scientific literature from published papers.

2 | MATERIALS AND METHODS**2.1 | Inclusion criteria**

The inclusion criteria for the investigated biologics were:

- Approved by EMA from 1 January 1999 to 31 December 2018.
- Indicated for rheumatologic or inflammatory bowel diseases.

Initial available data at the time of authorization for the selected biologics were investigated. The data were extracted by one investigator (N.G.) from the oldest publicly accessible "Initial scientific discussions" in the European Public Assessment Reports (EPARs) for each biological from the EMA official website.¹¹ The extracted information used in these comparisons is from the

What is already known about this subject

- At the time of launching biologics the effects on reproduction/lactation are unknown although many patients that receive these drugs are of reproductive age. Because the effects are unknown, pregnancy during the use of these drugs is discouraged. It is expected that after launch pharmaceutical companies will actively update the results of pregnancy/lactation outcomes.

What this study adds

- Our study gives a perspective on the pre- and post-authorisation data on pregnancy/lactation provided for different biologics at the same indication range. It shows the differences between regulatory and clinical approaches to this issue. It also creates a paradigm for future studies of optimizing regulations regarding (contra) indication of biologics during pregnancy/lactation.

sections in the initial dossiers discussed in the EPARs called "Reproduction Toxicity", "Toxico-pharmacological aspects" and "Toxicokinetics".¹²⁻²⁸

The data added during the post marketing period were extracted from the latest versions (to 7 May 2019) of the Summary of Product Characteristics (SmPCs). The additional post-marketing data were considered as the data related to pregnancy and/or lactation not mentioned in the initial dossiers but mentioned in the latest version of SmPCs in the sections "4.6 Fertility, pregnancy and lactation" and "5.3 Preclinical safety data".²⁹⁻⁴⁴

2.2 | Pregnancy information sections

The provided information was categorized as follows: (a) pre-clinical/animal studies, (b) human female fertility, (c) pregnancy-related outcomes, (d) congenital malformations in the human fetus and (e) recommendations regarding continuation and/or discontinuation during pregnancy Table 1.

The data per category were considered adequate when they fulfilled the following criteria (shown in green in Tables 2 and 3):

1. Pre-clinical/animal studies: When the requirements of the ICH-S5 and ICH-S6 guidelines are fulfilled during the pre-marketing period.^{6,8}
2. Human female fertility: When data is provided on evaluation of human female fertility by measuring effects on

TABLE 1 Provided clinical data and subsequent SmPC recommendations on the use of adalimumab, certolizumab pegol, etanercept and infliximab during pregnancy

Biological	Data	Latest SmPC recommendations
Adalimumab	2100 prospectively collected exposed pregnancies, no increased rate of malformations or other unfavourable outcomes*	"Adalimumab should only be used during pregnancy if clearly needed."
Certolizumab pegol	500 prospectively collected exposed pregnancies, no increased rate of malformations or other unfavourable outcomes*	"Cimzia should only be used during pregnancy if clinically needed."
Etanercept	Two observational cohorts, which have shown two different conclusions regarding major birth defects (adjusted OR 2.4 and 0.96 in 370 and 425 prospective cases, respectively) but no increased rate of other unfavourable outcomes*	"Enbrel should only be used during pregnancy if clearly needed."
Infliximab	1100 prospectively collected exposed pregnancies, no increased rate of malformations but increased risk for secondary outcomes**	"Infliximab should only be used during pregnancy if clearly needed."

*Unfavourable outcomes in this regard include spontaneous abortions, minor birth defects, preterm delivery, birth size and serious or opportunistic infections and no stillbirths or malignancies.

**Including Caesarean section, preterm birth, small for gestational age and low birth weight.

hypothalamic/pituitary gonadal function, as well as effects on the reproductive organs/tissues, eg, by measuring serum prolactin, Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), progesterone, oestrogen levels and thyroid function.⁵

3. Pregnancy-related outcomes: When prospective data on human pregnancy outcomes, with the exception of congenital malformations (which are considered under (d)), are provided.
 - a. During the pre-marketing period, adequacy is considered as delivering the results of unplanned pregnancies during clinical trials in initial dossiers.

- b. In the post-marketing period adequacy is considered as reflecting information from spontaneous reports and publications in the literature on exposed pregnancy outcomes in the most up to date SmPC, additional to the data delivered in the initial dossier.⁴ Retrospective data are considered as supportive information but not adequate.

4. Congenital malformations in the human fetus:
 - a. When during the pre-marketing period the results of unplanned pregnancies are specifically mentioned regarding congenital malformations.
 - b. When during the post-marketing period at least 300 pregnancies exposed during the first trimester are prospectively studied and a clear description of the incidences and type of congenital malformations is given. The number of 300 patients is necessary to be able to exclude the ≥ 10 -fold risk of major congenital malformations compared to the general population.⁵ In addition, when the assessment of fetal and/or neonatal toxicity for second/third trimester or pre-partum exposures are provided based on available prospective or retrospective data, this is also considered in this section as supportive information but not adequate.²⁸

When supportive information is only delivered by marketing authorization holders (MAHs), this is shown in red in Tables 2 and 3. Orange colour in Tables 2 and 3 is considered as a symbol of being for a short time (< 5 years) in the market, adequacy of data for clinical management based on mentioned specific definitions, wouldn't apply in these cases for post-marketing period.

2.3 | Lactation information sections

Regarding lactation the data was divided into three categories for each biological: pre-clinical/animal studies, excretion in human breast milk and absorption in children.

Data were considered adequate for clinical management when they fulfilled the following criteria (shown in green in Tables 2 and 3), stratified according to section:

1. Pre-clinical and/or animal studies: When the amounts and timing of drug concentration in the mother's milk of studied animals are provided.⁴⁵ As larger molecules such as immunoglobulins have more chance of being secreted into the milk due to larger gaps in breast alveolar cells during the first postpartum days, the timing of sampling is crucial for adequacy of information in this regard.⁴⁶ The statement of being detectable/undetectable in mother's milk in animals without exact amounts of excretion or the below the limit of quantitation (BLQ) levels is considered as supportive information but not adequate (transparency issue).
2. Excretion in human breast milk: When the concentration of the active substance in human milk is estimated.⁵

TABLE 2 Results regarding pre/post-marketing data published by the EMA on biologics use during pregnancy

Section	Data	Abatacept	Adalimumab	Anakinra	Belimumab	Canakinumab	Certolizumab	Etanercept	Golimumab	Infliximab
Pre-clinical/animal studies	Pre*									
Human female fertility	Pre									
	Post**									
Pregnancy-related outcomes	Pre									
	Post									
Congenital malformations in the human fetus	Pre									
	Post									
Years in the market		~12	~16	~17	~8	~10	~10	~19	~10	~20

TABLE 2 (Continued)

Section	Data	Ixekizumab	Rituximab [∞]	Sarilumab	Secukinumab	Tocilizumab	Ustekinumab	Vedolizumab
Pre-clinical/animal studies	Pre*							
Human female fertility	Pre							
	Post**							
Pregnancy-related outcomes	Pre							
	Post							
Congenital malformations in the human fetus	Pre							
	Post							
Years in the market		~3	~21	~2	~5	~10	~10	~5

Abbreviations: Pre, pre-marketing period; Post, post-marketing period.

Green: adequate data for clinical management; red: inadequate data for clinical management; orange: in the market for a short time (< 5 years), adequacy of data for clinical management was considered based on a specific definition, which is discussed in Material and Methods wouldn't apply in these cases.

∞For rituximab, animal studies on pregnancy were done in cynomolgus monkeys, during the post-marketing period.

*Pre: Pre-marketing period.

**Post: Post-marketing period.

TABLE 3 Results regarding pre/post-marketing data published by EMA on biologics use during lactation

Section	Data	Abatacept	Adalimumab	Anakinra	Belimumab	Canakinumab	Certolizumab	Etanercept	Golimumab	Infliximab
Pre-clinical/animal studies	Pre*									
Excretion in human breast milk	Pre									
	Post									
Absorption in children	Pre									
	Post									
Years in the market		~12	~16	~17	~8	~10	~10	~19	~10	~20

TABLE 3 (Continued)

Section	Data	Ixekizumab	Rituximab	Sarilumab	Secukinumab	Tocilizumab	Ustekinumab	Vedolizumab
Pre-clinical/animal studies	Pre*							
Excretion in human breast milk	Pre							
	Post							
Absorption in children	Pre							
	Post							
Years in the market		~3	~21	~2	~5	~10	~10	~5

Pre, pre-marketing period; Post, post-marketing period.

Green: adequate data for clinical management; red: inadequate data for clinical management; orange: only been on the market for a short time (<5 years), adequacy of data for clinical management was considered based on a specific definition, discussed in Material and Methods, which wouldn't apply in these cases.

*Etanercept and rituximab provided animal studies on lactation during the post-marketing period.

3. Absorption in children: When the amount of medicinal product received by infants via milk is estimated based on the infant dose as a percentage of the weight-adjusted maternal dose. If this is <10% no additional studies are required. If the percentage of weight-adjusted maternal dose exceeds 10%, breastfed infants' plasma concentrations of the medicinal product, it should be studied and follow-up studies of the breastfed children should be initiated.^{45,47}

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the The International Union of Basic and Clinical Pharmacology/British Pharmacological Society (IUPHAR/BPS) Guide to Pharmacology.

3 | RESULTS

Based on the inclusion and exclusion criteria the following 16 biologics were included (named alphabetically):¹¹⁻⁴⁴

1. **abatacept** (Orencia, Date of authorization: 21/05/2007, Indications: Rheumatoid Arthritis (RA), polyarticular Juvenile Idiopathic Arthritis (pJIA), Psoriatic Arthritis (PsA), Mechanism of action: T-cell inhibition),
2. **adalimumab** (Humira, Date of authorization: 07/09/2003, Indications: Ankylosing Spondylitis (AS), Uveitis, Ulcerative Colitis (UC), Psoriasis, PsA, Crohn's Disease (CD), pJIA, RA, Mechanism of action: tumor necrosis factor (TNF) inhibition),
3. **anakinra** (Kineret, Date of authorization: 08/03/2002, Indication: RA, Mechanism of action: Interleukin (IL)-1 inhibition),
4. **belimumab** (Benlysta, Date of authorization: 13/07/2011, Indication: Systemic Lupus Erythematosus, Mechanism of action: B-cell inhibition),
5. **canakinumab** (Ilaris, Date of authorization: 23/10/2009, Indications: Periodic fever syndromes, Still's disease, Gouty arthritis, Mechanism of action: IL-1 inhibition),
6. **certolizumab pegol** (Date of authorization: 01/10/2009, Indication: RA, Mechanism of action: TNF inhibition),
7. **etanercept** (Enbrel, Date of authorization: 02/02/2000, Indications: AS, pJIA, PsA, Psoriasis, RA, Mechanism of action: TNF inhibition),
8. **golimumab** (Simponi, Date of authorization: 01/10/2009, Indications: PsA, AS, UC, RA, Mechanism of action: TNF inhibition),
9. **infliximab** (Remicade, Date of authorization: 13/08/1999, Indications: AS, RA, Psoriasis, CD, UC, PsA, Psoriasis, Mechanism of action: TNF inhibition),
10. **ixekizumab** (Taltz, Date of authorization: 25/04/2016, Indications: Plaque psoriasis, PsA, Mechanism of action: IL-17 inhibition),

11. **rituximab** (MabThera, Date of authorization: 02/06/1998, Indications: Non-Hodgkin Lymphoma, Chronic B-Cell Lymphocytic Leukemia, RA, Mechanism of action: B-cell depletion),
12. **sarilumab** (Kevzara, Date of authorization: 23/06/2017, Indication: RA, Mechanism of action: IL-6 inhibition),
13. **secukinumab** (Cosentyx, Date of authorization: 14/01/2015, Indications: PsA, Psoriasis, AS, Mechanism of action: IL-17 inhibition),
14. **tocilizumab** (RoActemra, Date of authorization: 15/01/2009, Indications: RA, pJIA, Mechanism of action: IL-6 inhibition),
15. **ustekinumab** (Stelara, Date of authorization: 15/01/2009, Indications: Psoriasis, PsA, Crohn Disease, Mechanism of action: IL-12/23 blockade),
16. **vedolizumab** (Entyvio, Date of authorization: 22/05/2014, Indications: UC, CD, Mechanism of action: T-cell inhibition).

The results for initial data based on the definitions of adequacy criteria in each section are shown in Table 2 (for more detailed information see Supporting Information Table S2A):

1. Pregnancy data

a. Pre-clinical and/or animal studies:

For abatacept, adalimumab, anakinra, belimumab, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, sarilumab, secukinumab, tocilizumab, ustekinumab and vedolizumab, animal studies on reproduction were performed during the pre-marketing period. For rituximab, no reproductive pre-clinical/animal studies were mentioned to have been performed before marketing authorization. All the biologicals except rituximab therefore scored as adequate in this section. No additional data were provided in the most up to date SmPC of adalimumab, anakinra, belimumab, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab, tocilizumab, ustekinumab and vedolizumab. Data for embryo-fetal development studies for abatacept are provided in the latest version of the SmPC and do not show "unfavorable effects" (the definition of "unfavorable effects" is not given). Studies were done in cynomolgus monkeys for rituximab during the post-marketing period which show depletion of B cells in peripheral blood and in lymphoid tissue in the fetus.¹²⁻⁴⁴

b. Human female fertility:

Pre-marketing period: For abatacept, adalimumab, anakinra, belimumab, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, ustekinumab and vedolizumab no studies were performed to evaluate effects on human female fertility.¹²⁻²⁸

Post-marketing period: No additional fertility studies to investigate effects on women's fertility were performed for the 16 biologicals. Consequently, none of them scored as adequate in this section.²⁹⁻⁴⁴

c. Pregnancy-related outcomes:

Pre-marketing period: Results of unplanned pregnancies during clinical trials were provided for abatacept, ixekizumab, sarilumab and secukinumab (for detailed information see Supporting Information Table S2A). For belimumab 60 unplanned pregnancies during clinical trials occurred. The results of these unplanned pregnancies were not provided. For adalimumab, anakinra, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, ustekinumab and vedolizumab no information was provided on whether there were unplanned pregnancies during the clinical trials.¹²⁻²⁸

Post-marketing period: For abatacept, anakinra, belimumab, canakinumab, golimumab, rituximab, secukinumab, tocilizumab, ustekinumab and vedolizumab pregnancy-related studies are not provided in the SmPC for the post-marketing period.^{30-32,34-44} For adalimumab, certolizumab pegol, etanercept and infliximab prospective studies were conducted, including more than 300 followed pregnancies (for more details see Supporting Information Table S2A).²⁹⁻⁴⁴

d. Congenital malformations in the human fetus:

Pre-marketing period: Congenital malformations in unplanned pregnancies were not investigated during clinical development of abatacept, adalimumab, anakinra, belimumab, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, rituximab, sarilumab, tocilizumab, ustekinumab and vedolizumab. For secukinumab congenital malformations were investigated for unplanned pregnancies during clinical trials and none were found, therefore none of these biologicals were scored as adequate for clinical management in this section except secukinumab.¹²⁻²⁸

Post-marketing period: No prospective studies were performed to investigate congenital malformations in pregnancies exposed to abatacept, anakinra, belimumab, canakinumab, golimumab, rituximab, secukinumab, tocilizumab, ustekinumab and vedolizumab during the post-marketing period, and spontaneous reporting was relied on instead.²⁹⁻⁴⁴

Adalimumab, certolizumab pegol and etanercept initiated registries regarding pregnancy-related outcomes and congenital abnormality risk anticipation during the post-marketing period. For infliximab one controlled observational study was conducted during the post-marketing period. The results of these studies are briefly mentioned in the latest SmPCs (see the Appendix).^{36,38,39,43} These biologics scored as delivering adequate data for clinical management in this section. Recommendations have changed in the most updated SmPCs based on these studies (Table 1).

The results for initial data regarding investigated three categories in lactation is shown in Table 3. Based on the definitions of adequate for clinical management in each section, each investigated biological was scored as bellow (for detailed comparison please see Supporting Information Table S3A in the Appendix):

2. Lactation data

a. Pre-clinical and/or animal studies:

The results of drug concentration in breast milk in pre-clinical/animal studies during the pre-marketing period were provided for following biologicals:

- Abatacept: In lactating rats, the milk-to-serum ratios for abatacept were 0.08-0.09. Abatacept was also detected in pup sera but the origin of this activity is unclear (from maternal milk or from maternal circulation). The lower limit of quantification (LLQ) for abatacept in rat milk was 3.0 ng/mL. The calibration range was in the range 1-40 ng/mL.²⁸
- Belimumab: This was detected in milk from female monkeys administered 150 mg/kg every 2 weeks. The exact amounts of detected drug are not provided.²⁵
- Certolizumab pegol: Administration of the full antibody resulted in exposure of rats' offspring via milk. Milk transfer was negligible.²⁴
- Golimumab: This was found in monkey breast milk, but the concentrations were low (4 µg/mL in the 50 mg/kg treatment group) and were approximately 350-fold lower than maternal serum concentrations during the lactation period.²²
- Ixekizumab: This was excreted at low levels in the milk of cynomolgus monkeys. The maternal milk to maternal serum concentration ratios in cynomolgus monkeys were 0.0018 and 0.0011 for doses of 5 mg/kg and 50 mg/kg, respectively on postpartum day (PPD) 14. Mean Ixekizumab milk concentrations decreased over time to PPD 56.¹⁴
- Ustekinumab: Excretion at low levels in cynomolgus monkeys was detected, but the exact amounts of detected drug and timing of sample acquisition are not provided.¹⁷
- Vedolizumab: Low levels (<300 mcg/L) on day 28 postpartum in breast milk in 3/11 animals at dosage of 100 mg/kg. Not detected in the breast milk at 10 mg/kg.¹⁶

Timing of sample acquisition was only mentioned for ixekizumab and vedolizumab, therefore based on mentioned criteria these biologicals scored as adequate for pre-clinical/animal studies delivery criteria. No animal studies were performed to measure drug secretion into mother's milk in initial trials of adalimumab, anakinra, canakinumab, etanercept, infliximab, rituximab, sarilumab, secukinumab and tocilizumab, therefore data for these biologicals scored as not adequate for initial data on pre-clinical/animal studies.¹²⁻²⁸ During the post-marketing period drug concentrations in mother's milk in animal studies were provided for etanercept (excreted in rat milk and in the serum of pups, the exact amounts and timing of detected drug are not provided) and rituximab (detectable in milk from lactating monkeys, the exact amounts and timing of detected drug are not provided). For adalimumab, anakinra, canakinumab, infliximab, ixekizumab,

sarilumab, secukinumab and tocilizumab, there are no data available in this regard.²⁹⁻⁴⁴

b. Excretion in human breast milk:

Pre-marketing period: The concentration of the active substance/metabolites in human milk was not determined for any of the investigated biologicals before marketing authorization.¹²⁻²⁸

Post-marketing period: The concentration of the active substance/metabolites in human milk was estimated for adalimumab (a literature review by the manufacturer indicated low excretion of adalimumab in breast milk) and certolizumab pegol (minimal transfer to breast milk in 17 lactating women) during the post-marketing period. None of other investigated biologicals delivered data in this regard during the post-marketing period.²⁹⁻⁴⁴

c. Absorption in children:

Pre-marketing period: The estimated amount of medicinal product received by infants via milk was not calculated for any of the investigated biologicals before marketing authorization.¹²⁻²⁸

Post-marketing period: The amount of medicinal product received by infants via milk was estimated for certolizumab pegol (0.04-0.30%) and adalimumab (0.1-1%) based on the infant dose as a percentage of the weight-adjusted maternal dose. In both these amounts were <10% and therefore no additional studies were required based on mentioned criteria (see Materials and Methods). No other investigated biologicals delivered data in this regard during the post-marketing period.²⁹⁻⁴⁴

All together, initial data could not be scored as adequate for clinical management for the investigated biologics in any of the categories for any of the investigated biologics other than animal studies on lactation for abatacept, belimumab, certolizumab pegol, golimumab, ixekizumab, ustekinumab and vedolizumab (seven out of 16 investigated biologics). Only adalimumab and certolizumab pegol provided adequate data during the post-marketing period on excretion in human breast milk and absorption in children. These are also the only two biologics approved by the EMA for use during lactation. The most recent dossier on adalimumab does not provide data on concentration of adalimumab in breast milk in animal studies.^{39,43}

4 | DISCUSSION

Despite being on the market for years, the data on pregnancy and lactation outcomes are still not adequately delivered for most of the investigated biologicals. The clinical relevance of most of these biologicals could not be scored as sufficient for making an evidence-based decision in practice. Comparing the pre- and post-marketing data shows in general inadequate efforts for providing information in this regard. Clinicians therefore have to make decisions without supporting data in this regard, even after years of marketing authorization. This can lead to unnecessary discontinuation of biologics or unnecessary termination of pregnancy. At the time of marketing

authorization the only available data that can be used to estimate a risk during pregnancy are animal data and data on unplanned pregnancies during clinical trials. As pointed out in ICH-S6 guideline,² reproduction toxicity studies in animals should only be performed if the product of interest is pharmacologically active in the animal species, as most if not all of the adverse effects seen are due to the pharmacological effect. For biologicals, the species used is often the monkey, as this is the only relevant species in most cases due to specificity of the compound. A lack of adverse effects in the monkey does not translate into a guarantee of safety in humans, although it does provide some reassurance. However, adverse effects that can be related to the mechanism of action of the biological on embryo-fetal development in the monkey can be seen as a clear signal for risk during human pregnancy. Further clinical data are required in any case to provide a clear understanding of the risk and allow clinical management of patients with a reproductive wish during the treatment of autoimmune inflammatory diseases with biologics.

The problem regarding lack of adequate pregnancy/lactation data extends even further, since after years of being in the market limited initiatives from the pharmaceutical companies have been taken for collecting prospective data during pregnancy or publishing the available data from their databases. Post-marketing data on pregnancy exposure submitted by the marketing authorization holders (such as periodic safety update reports) are mostly retrospective and inconclusive. Risk minimization measures are inadequate and most of the time ineffective. However, for adalimumab, certolizumab pegol and etanercept, pharmaceutical companies updated information and as a result adjustments were made in their SmPCs (AbbVie, one of the sponsors for the adalimumab pregnancy exposure registry, and Amgen, the main sponsor of the etanercept pregnancy registry cohort study, both conducted by the Organization of Teratology Information Specialists, UCB Pharma as the main sponsor of the CRIB and CRADLE pharmacokinetic studies).⁴⁸ If initiating registries and follow-up studies about exposure to biologicals during pregnancy and/or lactation were mandatory, the same could be done by other MAHs.

After reviewing all our data it seems that intensified collaboration between healthcare providers, academics and MAHs to enhance research on reproduction/lactation at an early stage of biological development is needed. This responsibility includes all stakeholders.

4.1 | Suggestions for future legalisation procedures

In view of the current non-optimal situation, we suggest the following:

4.2 | Pre-clinical investigations:

1. Investment in the development of human-relevant technologies should be made in addition to existing animal studies. From

human-relevant technologies we can refer to micro-engineered models of the human placental barrier to simulate and investigate drug transfer from maternal to fetal circulation, in vitro perfusion studies of human placentas obtained immediately after delivery and bioluminescent imaging of drug efflux activity at the blood-placenta barrier. From a regulatory point of view, this evidence may or may not change the benefit-risk assessment of the product, but it would be useful when clinical data are not available. Existing technologies can be used in this regard, eg, conducting cell biology research to investigate binding and functional consequences for different cell types in the human placenta.⁴⁹⁻⁵⁴

2. More focus is needed on the timing of the transfer of the biological during lactation. Samples should be taken within the first week of lactation and at several time points afterwards to investigate the hypothesis that transfer to breast milk is only relevant for colostrum.

4.3 | During clinical trials:

1. Unplanned pregnancies during randomised controlled trials should be documented, each case should be followed up and appropriate documentation of the outcomes should be amended (taking into consideration that many women make a choice for elective abortion). This provides stronger evidence than retrospective data in initial states and should be performed in addition to gathering prospective post-marketing data.
2. The children of those unplanned pregnancies should be followed up and their development and growth documented. Data on transfer to breast milk should be collected when available.

4.4 | Post-marketing period:

1. The minimum data to be delivered by the marketing authorisation holder about pregnancy/lactation should be defined precisely. This should be collected as additional pharmacovigilance activity next to spontaneous reporting, with strict milestones regarding submission of data.
2. The initiation of pregnancy registries should be imposed on marketing authorisation holders as an additional pharmacovigilance activity (collecting prospective data), with milestones on interim reporting (this point can also be applied to the pre-marketing period).
3. Missing pregnancy/lactation data should not be a routine statement in Risk Management Plans (RMPs) and there should be amendments for planning an active approach in this regard.
4. Academic researchers should be allowed to have access to data on biological exposure during pregnancy/lactation from clinical trials and post-marketing data collected by pharmaceutical companies. Additional cooperation between databases of medicines regulatory

networks such as Eudravigilance and databases of pharmaceutical companies should be facilitated.

MAHs and regulatory authorities should reflect all the available data about pregnancy and lactation that is clearly related to the use of the biological in detail and numerically in SmPC and EPAR public assessment reports. Limiting the given information to conclusions and interpretations should be therefore avoided.

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COMPETING INTERESTS

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CONTRIBUTORS

C.J.VdW. conceived of the presented idea, reviewed the draft versions, gave input and supervised the project. N.G. developed the theory, performed the search and wrote the drafts and final manuscript. R.J.E.M.D. helped supervise the project, reviewed the draft versions and gave input. C.L.E.S., J.W.vdL. and H.J.C. helped to develop the initial idea, reviewed the draft versions and gave input. J.M.W.H. reviewed the draft versions and gave input. E.P.VP. reviewed the final manuscript and gave input. All authors discussed the results and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available on the European Medicines Agency's website at <http://www.ema.europa.eu>.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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